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Study protocol for a multicentre, randomised controlled trial to compare the use of the decellularised dermis allograft in addition to standard care versus standard care alone for the treatment of venous leg ulceration: DAVE trial

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ABSTRACT

Introduction Venous leg ulceration (VLU), the most common type of chronic ulcer, can be difficult to heal and is a major cause of morbidity and reduced quality of life. Although compression bandaging is the principal treatment, it is time-consuming and bandage application requires specific training. There is evidence that intervention on superficial venous incompetence can help ulcer healing and recurrence, but this is not accessible to all patients. Hence, new treatments are required to address these chronic wounds. One possible adjuvant treatment for VLU is human decellularised dermis (DCD), a type of skin graft derived from skin from deceased tissue donors. Although DCD has the potential to promote ulcer healing, there is a paucity of data for its use in patients with VLU.

Methods and analysis This is a multicentre, parallel group, pragmatic randomised controlled trial. One hundred and ninety-six patients with VLU will be randomly assigned to receive either the DCD allograft in addition to standard care or standard care alone. The primary outcome is the proportion of participants with a healed index ulcer at 12 weeks post-randomisation in each treatment arm. Secondary outcomes include the time to index ulcer healing and the proportion of participants with a healed index ulcer at 12 months. Changes in quality of life scores and cost-effectiveness will also be assessed. All analyses will be carried out on an intention-to-treat (ITT) basis. A mixed-effects, logistic regression on the outcome of the proportion of those with the index ulcer healed at 12 weeks will be performed. Secondary outcomes will be assessed using various statistical models appropriate to the distribution and nature of these outcomes.

Ethics and dissemination Ethical approval was granted by the Bloomsbury Research Ethics Committee (19/LO/1271). Findings will be published in a peer-reviewed journal and presented at national and international conferences.

Trial registration number ISRCTN21541209.

Strengths and limitations of this study

- This is the first randomised controlled trial evaluating the use of the decellularised dermis (DCD) allograft solely in patients with venous leg ulceration (VLU).
- The cost-effectiveness analysis will assess the economic impact of using the DCD allograft for the management of patients with VLU.
- This is a pragmatic study hence compression and debridement technique will be up to local guidelines/standard care.
- This study only evaluates applications in patients with chronic venous ulceration.
- This study does not address long-term recurrence rates beyond 1 year.

INTRODUCTION

Background and rationale

Venous leg ulceration (VLU) describes a persistent wound in the lower limbs caused by a poorly functioning venous system. Characterised by chronicity and a protracted and intensive treatment, these wounds affect approximately 1%–2% of the population, with prevalence increasing to up to 4% in those over 65 years of age.[1 2]

VLU has a devastating impact on quality of life (QoL) and social function especially in

the elderly.[3–5] The wounds can be very painful, resulting in reduced mobility, and require regular dressing changes, which can be extremely painful and time-consuming. Together, these factors result in negative QoL effects as severe as those seen in other life-limiting chronic conditions, such as congestive cardiac failure and chronic obstructive pulmonary disease.[6]

VLU presents a significant burden to the healthcare service.[7] Up to 50% of district nurse time is spent caring for people with chronic wounds, of which 70% will be venous in origin.[8 9] Furthermore, ulcers can recur many times with up to 48% recurring at 5 years, thus requiring further treatment.[10 11] Combined with the social cost due to loss of work and productivity, VLU is estimated to cost up to 2% of the annual healthcare budget, which equates to approximately £2.5 billion in the UK in 2017.[12] This is predicted to increase as a result of the ageing population.[13]

The management of chronic VLU is therefore an important priority and public health concern. Compression, in the form of bandaging and stockings, is the underlying principle of treatment, with the aim of reducing venous hypertension.[14] However, applying compression is time-consuming; bandage application requires skill and stockings are not suitable for everyone.[14 15] Furthermore, the reduction in community nursing numbers has resulted in increasing difficulty for patients to access this service.[16 17]

Evidence from the ESCHAR and EVRA trials shows that interventions to abolish superficial venous incompetence improve ulcer healing and recurrence.[8 18] Although promising, such intervention is not accessible to all patients.[19] Moreover, although EVRA reported that early intervention performed in ulcers with a duration of less than 6 months was beneficial, many patients present within leg ulceration of greater duration than this, recurrent ulceration despite eradication of venous incompetence or may have underlying deep venous incompetence. These chronic wounds are known to be hard to heal and require considerable nursing resources.[10 20] The current treatments offered are therefore insufficient for the management of VLU.

Skin grafting represents an adjuvant treatment that can promote and expedite ulcer healing.[21] Grafts can be taken from the patient's own skin, from a donor or from tissue-engineered skin.[22] An autograft (graft from own skin) can be performed in different ways, including pinch and punch grafting, mincing and meshing.[23] Despite promoting ulcer healing, drawbacks exist, including poor cosmetic outcomes and the need for a formal surgical procedure in an operating theatre in some instances.[24 25] Furthermore, surgical waiting lists can be lengthy and, in the current National Health Service (NHS) climate, bed availability is not guaranteed.[26] Thus, routine autografts are not accessible to all patients with ulcer. Allografts (donor skin) and xenografts (animal skin) have been successfully employed, but present similar drawbacks to autografts and the potential for immunogenicity and disease transmission.[27] Tissue-engineered skin is donor skin that has been processed to be made inert, and therefore is not immunogenic.[28] A Cochrane review found that tissue-engineered skin in conjunction with compression increased the healing rate in venous ulceration; however, there was insufficient evidence to determine the effectiveness of any other skin graft material.[29]

Human decellularised dermis (DCD) is generated from skin donations from deceased tissue donors processed to remove epidermal and dermal cells while preserving dermal structures and is supplied nationally by the NHS Blood and Transplant (NHSBT).[30 31] This provides an immunologically inert scaffold to support cellular repopulation and tissue revascularisation. Although allografts can only serve as temporary cover, the advantage of the DCD allograft is that it can be applied to the wound with local anaesthesia (via tissue staples or sutures) or without (via tissue glue), and therefore does not require admission for a procedure under general anaesthetic. The procedure can be performed in the outpatient department, avoiding inpatient admission and theatre use, making the technique more accessible to a larger group of patients.

The majority of DCD studies, including randomised controlled trials, have been performed in populations with diabetes.[32–35] DCD allografts have been reported as safe, to promote angiogenesis[36] and, in randomised controlled trials, to significantly reduce ulcer healing time (by up to 50%).[37 38] Cohort study data reveal a reduction in wound surface area, improved healing in venous ulceration, with evidence of angiogenesis, host cell migration and proliferation.[39] This study addresses the lack of robust research evidence about the effects of DCD allografts on VLU healing.

This prospective, randomised, open (non-blinded), pragmatic trial will explore whether the DCD allograft in addition to standard care, compared with standard care alone, will improve healing rates, reduce recurrence, increase ulcer-free time and improve QoL for those with VLU. In addition, a cost-effectiveness analysis will be performed to assess the economic impact of using the DCD allograft for the management of this patient population, whose care consumes significant financial resource.

Currently, the annual cost to conservatively manage VLU is approximately £1200 per patient[14] ; however, in chronic ulceration this is likely to be more. The NHS per patient costs for graft application will be approximately £400. If a positive outcome results from this trial, the reduced ulcer healing time will likely result in significantly reduced NHS costs with an improvement in quality-adjusted life years (QALYs).

Objectives

The primary objective is to determine whether the use of the DCD allograft in patients with VLU, in addition to standard care, improves healing at 12 weeks compared with standard care alone. Secondary objectives include comparisons of time to ulcer healing, change in ulcer

area at 12 weeks, ulcer recurrence at 12 months, QoL assessment at 12 weeks, 6 months and 12 months, and cost-effectiveness analysis.

METHODS AND ANALYSIS

Trial design

This is a prospective, randomised, open (non-blinded), pragmatic trial with a follow-up of 12 months.

Study setting

Eligible participants will be recruited from at least 10 sites in the UK. A full list of the study sites can be found on the International Standard Randomised Controlled Trial Number registry.[40]

Eligibility criteria

Inclusion criteria are: adult patients (>18 years), able to provide informed consent with a diagnosis of VLU with documented evidence of venous incompetence on duplex ultrasound, ulcer duration for >6 months and ulcer surface area ≥2 cm^2. Where there is more than one ulcer present, the largest ulcer will be chosen as the index ulcer for the purposes of the trial. Exclusion criteria include: a diagnosis of sickle cell disease, an Ankle Brachial Pressure Index <0.8, a clinically infected ulcer, treatment with biomedical or topical growth factors within the previous 30 days, and a history of an inability to tolerate compression therapy or a foot ulcer (ie, below the ankle). The DCD allograft preparation entails the use of a number of components, including specific antibiotics, which are then washed away. There have been no documented allergic or hypersensitivity reactions to the DCD graft reported. Patients with known allergies to the DCD preparation components are therefore able to participate at the discretion of the clinical team.

Interventions

All eligible patients will be informed about the study and provided with a written information sheet. Consenting participants will be randomised to receive either the DCD allograft in addition to standard care or standard care alone (figure 1). Baseline demographic data will be collected for each participant, including details of their medical history and any concomitant medication. The EQ-5D[41] and Charing Cross Venous Ulceration Questionnaire (CCVUQ)[42] will also be completed for generic and disease-specific QoL assessment, respectively.

Participants in the standard care arm will undergo wound cleaning and debridement, plus standard compression therapy in the form of multilayer elastic compression bandaging or stockings. Participants in the DCD arm will undergo wound cleaning and debridement and DCD allograft application. The DCD graft will be applied by trained registered healthcare professionals (physicians or nurses). Training on the application of the DCD graft will be provided by NHSBT. The DCD will be applied to the debrided index ulcer wound bed. Recommendations will be made that the DCD should be secured with surgical glue, staples and/or sutures to optimise graft adhesion. The DCD graft should be fenestrated liberally with a scalpel or scissors to allow wound exudate to pass through to reduce risk of seroma/haematoma developing under DCD. Following application of the DCD allograft, a non-adhesive, non-absorbent, non-medicated primary dressing will be applied, followed by the appropriate bolster/secondary dressings.[31] Compression therapy will then be applied according to local practice and may include multilayer elastic compression bandaging or stockings delivering 20–40 mm Hg pressure. Practice/district nurses will be advised not to change the primary dressing the first 7 days post-DCD allograft application. If the DCD allograft has not adhered to the wound bed at the 1-week visit, the graft can be rinsed in saline (if it appears viable) and reapplied and resecured. Additional grafts will not be reapplied as part of the trial.

As this is a pragmatic trial, the ulcer care in both arms will be as per local unit standard practice. All participants will have their ulcers irrigated, cleaned and debrided according to best local practice. Compression therapy will be according to local practice and may include multilayer elastic compression bandaging or stockings designed to deliver between 20 and 40 mm Hg pressure. Wound dressing and compression application will be performed by trained research nurses or community/district/practice nurses as per standard care. In the event of a missed visit, local study teams will liaise with/ask the participant to liaise with the district/community/practice nurse to arrange dressing change and compression application. The use of negative pressure wound therapy device will be left to the discretion of the treating clinician. All participants may be offered interventional procedures in the form of endovenous ablation (in the presence of superficial venous disease) dependent on whether local recruitment site practice is to intervene on ulcers over 6 months' duration. Once the wound has healed, the participant will be given a minimum of class II compression hosiery (18–24 mm Hg) to wear to prevent ulcer recurrence as per local practice. Endovenous ablation, among other procedures, at any point post-randomisation, will be recorded at the 12-month follow-up.

Primary outcome

The primary outcome is the proportion of participants with a healed index ulcer assessed with ulcer photography at 12 weeks after randomisation.

Secondary outcomes

The secondary outcomes include:

- Time to index ulcer healing from randomisation.
- The percentage change in index ulcer area at 12 weeks from randomisation.
- The proportion of participants with a healed index ulcer at 12 months from randomisation.

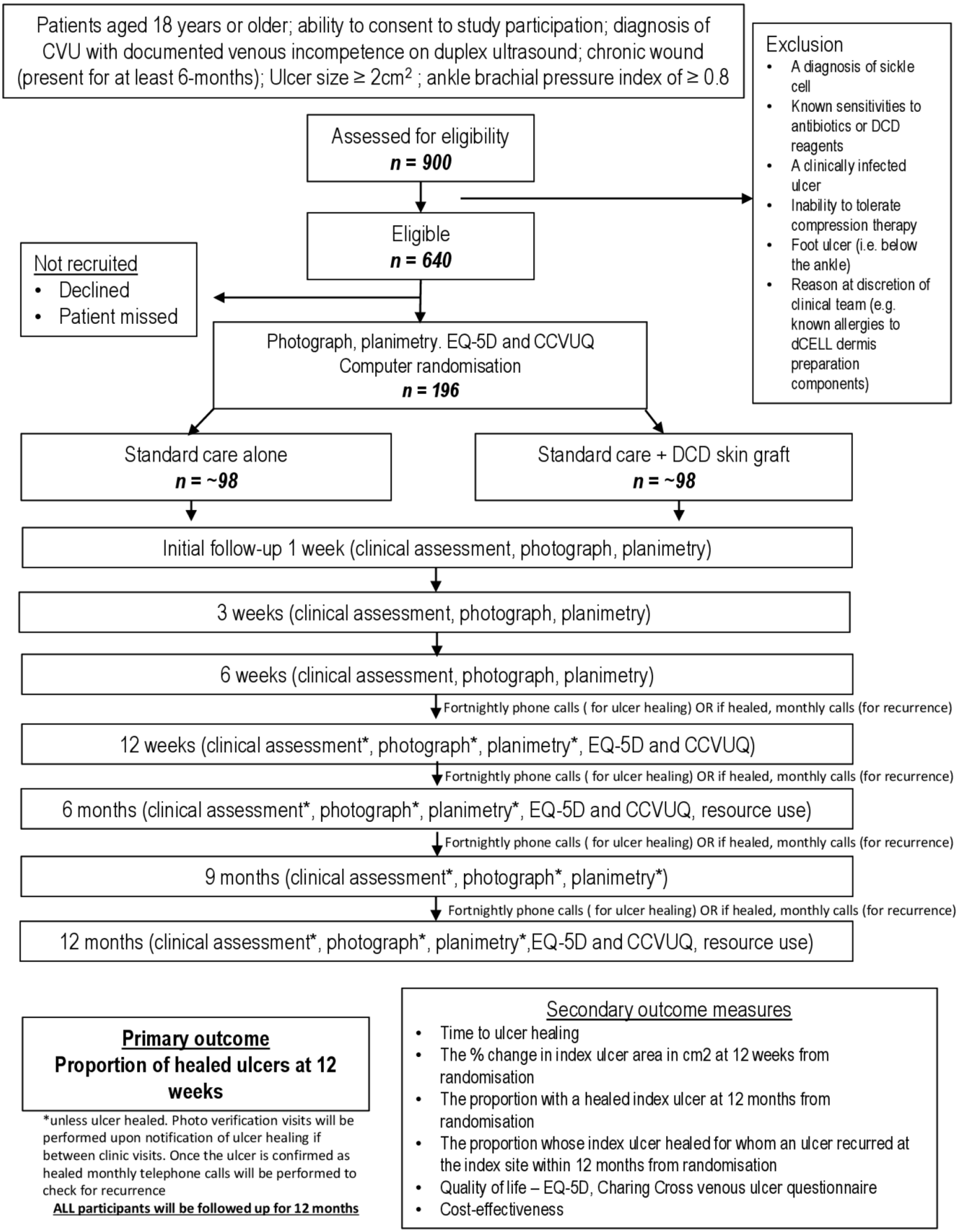

Figure 1 Flow diagram of the study protocol. CCVUQ, Charing Cross Venous Ulceration Questionnaire; CVU, chronic venous ulceration; DCD, decellularised dermis.

- The proportion of those whose index ulcer healed for whom an ulcer recurred at the index site within 12 months from randomisation.
- Change in QoL score at 12 weeks, 6 months and 12 months from randomisation using the EQ-5D and CCVUQ.
- Cost-effectiveness analysis, measured using the incremental cost-effectiveness ratio (ICER).

Sample size and study duration

To detect an absolute difference of 25% in the proportion of participants with a healed index ulcer at 12 weeks (assuming a healing rate of 30% in the control group and 55% in the intervention group) and allowing for a 10% loss to follow-up with a power of 90% and 5% level of significance, 196 patients are required (Stata/IC V.15.1 for Mac, Statacorp, College Station, Texas, USA; procedure 'power twoprop', with continuity correction). The effect size was estimated from previously published literature on diabetic and venous ulceration, showing an absolute difference in the proportion of participants with a healed ulcer of 25% between intervention and control groups at 12 weeks.[32 38 39] With the 12-month follow-up, this study will run for 36 months.

Interim analysis

When we have mature 12-week primary outcome data on the first 50 participants randomised, we will review the sample size with the independent Trial Steering Committee (TSC) on the basis of recruitment rate, the overall (blinded) primary outcome of index ulcer healed proportion (expected to be (30+55/2)=~40%) and attrition rate (expected to be 10%).

We plan on having a formal interim analysis with the possibility of stopping early for futility (no prospect of a clinically meaningful treatment effect, or for overwhelming evidence of effectiveness) at this point (of n=50 with mature primary outcome data, or at around 25% of the total scheduled events observed). This single interim analysis using a Lan-DeMets alpha spending approach with Fleming O'Brien boundaries has negligible effect on the required sample size (R V.3.4.1 for Windows, package gsDesign).

Recruitment

Potential participants will be identified at outpatient clinic appointments. Posters and leaflets will also be displayed in the outpatient clinics and other appropriate locations.

Potentially eligible patients will receive a verbal explanation of the study and a patient information sheet by the attending clinical/research team.

Randomisation

Consent forms are completed on the day of treatment. Following confirmation of eligibility, consent and completion of baseline assessments, participants will then be randomly allocated to receive one of the two possible treatment options using an online computerised web system (REDCap, managed by the study data centre, University of Edinburgh). A minimisation algorithm using centre, index ulcer size and duration will be used, including a random component to lessen predictability.

Blinding

As the DCD allograft is visible after application for a period of time, it is not possible to mask participants or the research/clinical teams to the treatment strategy. However, the primary outcome assessments (verification of index ulcer healing visits) will be completed by an independent clinical assessor trained in the assessment of wound healing, who will have no previous involvement with, or knowledge of, the participant's index ulcer treatment and as such will be blind to the randomised treatment strategy (the DCD allograft is not expected to be visible after 4 weeks).

Follow-up periods

All participants will attend for follow-up at 1 week, 3 weeks, 6 weeks and 12 weeks, 6 months, 9 months and 12 months post-randomisation. At all follow-up visits, a clinical assessment will be undertaken and a photograph and planimetry tracing of the ulcer will be collected (unless healing has been confirmed). The EQ-5D and the CCVUQ will be collected at baseline and the 12-week, 6-month and 12-month follow-ups. Healthcare-resource use (procedures, hospital, general practitioner and community nurse visits, physiotherapy and other interventions), days lost from work and normal activities, carer time and out-of-pocket expenses related to leg ulcer care will also be collected from case notes and patient diaries during the initial procedure and at 6 and 12 months.

Fortnightly calls will be made after the 6-week follow-up to check if the ulcer has healed. If the participant reports that their ulcer has healed, they will be invited to attend a verification visit, where a photograph of the ulcer will be taken. This photograph will be sent to an independent assessor (blinded to treatment allocation) for assessment and confirmation of healing status. Ulcer healing is defined as complete re-epithelialisation of the index ulcer in the absence of a scab (eschar) with no dressing required confirmed by blinded photo assessment of healing.

If the ulcer is confirmed as healed, monthly telephone calls will be performed to check for recurrence. In the event that an ulcer is confirmed as healed, the recurrence, safety, resource use and health questionnaire data can be collected over the telephone or by post. If the participant fails to attend their appointment, attempts will be made to collect the QoL and patient resource-use diaries by telephone or post. Participants will receive up to £10 for each visit attended as a contribution towards travel expenses.

Data collection and confidentiality

Participant data will be stored in the password-protected REDCap database. Participant details will be anonymised as each participant will be allocated a participant number.

Identifiable data, including contact information, will also be recorded on paper forms and will be kept in a locked filing cabinet in a locked office at each investigational site. Data will be monitored for quality and completeness and missing data will be requested from the participating sites, as per the data monitoring plan.

Statistical analysis

All analyses will be carried out on an intention-to-treat (ITT) basis. A mixed-effects, logistic regression on the outcome of the proportion of those with the index ulcer healed at 12 weeks, with site as a random effect and randomised group as the treatment effect, along with index ulcer size and duration at baseline (the minimisation factors) and any other baseline factors known or suspected to be strongly related to good or poor outcome, will form the model. Goodness of model fit will be examined using the Hosmer-Lemeshow approach. The robustness of the findings to any patterns of missing data (both assuming data are missing at random; and, if appropriate, informatively missing (missing not at random)) will be explored using appropriate sensitivity analyses.

Secondary outcomes (including the primary outcome at 12 months, time to index ulcer healing, reduction in ulcer area at 12 weeks, ulcer recurrence at 12 months and QoL) will be assessed using various statistical models appropriate to the distribution and nature of these outcomes, with the same modelling strategy as per the primary outcome above (eg, missing data and appropriate model diagnostics).

The proportion healed at 12 months and the recurrence of the index ulcer at 12 months will be analysed as the primary outcome above. The time to index ulcer healing will be analysed using a survival-type model (eg, Cox proportional hazards model), and if the assumption regarding proportional hazards fails, using a Restricted Mean Survival Time approach. The reduction in area of the index ulcer at 12 weeks over baseline will be analysed using a linear mixed model. The QoL data (EQ-5D and CCVUQ questionnaire) will be analysed using repeated measures mixed linear models (with repeated measures at 12 weeks, 6 months and 12 months and a suitable specified covariance structure), with the overall treatment effect and the evolution of any treatment effect over time modelled.

Cost-effectiveness analysis

A literature review will be conducted to identify other economic studies and other trials in comparable populations. A within-trial analysis and a decision model will be constructed. In both cases, the main analyses will be performed from the perspective of the NHS and Personal Social Services. Secondary analyses will be performed from a societal perspective. The price year will be 2018–2019. Discounting will be applied according to the UK government guidelines. The study will be reported according to Consolidated Guidelines for Economic Evaluation.[43]

The within-trial analysis will compare the treatment strategies within the 12-month time horizon of the clinical trial on an ITT basis. Data will be collected by case note review and questionnaires completed at baseline and follow-up.

Resource-use items in hospital and community care, adverse events (AEs) or complications will be recorded for each patient at 6 and 12 months. Resource use will be multiplied by UK unit costs obtained from published literature, Healthcare Resource Groups and manufacturers' list prices to calculate overall costs. Utilities and QALYs will be calculated from the EQ-5D questionnaire. The extent of missing data will be assessed and appropriate methods to handle missing data will be applied.

The decision model provides a framework to incorporate evidence from other relevant studies and to extrapolate outcomes, such as ulcer healing and recurrence, beyond the trial reporting period. The Markov model will include the key ulcer-related health states and events that may occur during the lifetime of the patient. The data to support extrapolation may be taken from the trial (eg, fitting parametric time-to-event functions to the trial data) or may come from external sources (such as the literature review or observational data).[44 45]

In both the within-trial and model analyses, the ICER will be calculated and compared with current UK decision-making thresholds. Sensitivity analysis will be carried out to test the robustness of results to alternative assumptions about model structure or data. The cost-effectiveness acceptability curve will be calculated using probabilistic sensitivity analysis.[43]

Data monitoring, safety and quality control

An independent TSC and independent Data Monitoring Committee (iDMC) have been appointed. The main role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice and the relevant regulations, while the main role of the iDMC is to safeguard the interests of trial participants and to monitor the main outcome measures including safety and efficacy. A clinical trial manager, together with the Trial Management Group, will oversee trial progress.

All treatment-related AEs (related to the skin graft or leg ulcer only) will be collected as will all serious AEs (SAEs). The chief investigator (CI) will be notified of all SAEs within 24 hours. All SAEs will be reported to the research ethics committee if, in the opinion of the CI, the event was related to the intervention. All related AEs and SAEs will be recorded and summarised by treatment strategy. These analyses will be descriptive, with any p values calculated to be interpreted descriptively.

DISCUSSION

Although compression therapy is the mainstay of treatment, there is a need to explore new treatments for wounds that are chronic and persistent in nature. This is

the first randomised controlled trial to evaluate the use of DCD allograft for the treatment of VLU. This study will provide important data on whether the use of the DCD allograft plus standard care is associated with improved outcomes compared with standard care alone and will provide important data on its effects on QoL and healthcare costs.

Patient and public involvement

Focus groups were held with patients accessing the vascular clinic at Imperial College Healthcare NHS Trust to obtain views on the proposed study and the acceptability of the DCD allograft. The focus group helped to inform important aspects of the trial, including the number of visits and questionnaires used in the study. A Patient and Public Involvement (PPI) representative was included as a co-applicant and provided invaluable input in the study design. A PPI representative also sits on the TSC, providing real-time input on study progress. He will also aid with dissemination of the results.

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Contributors AHD, SO, TL, FH and LB were involved in the design of the study and securing funding. MG, KP, NC, AB and KD were involved in the design of the study. AHD, SO and FH drafted the protocol and applied for ethical approval. AHD and SO supervise the project. FH and SP coordinate the project. SO, AHD and SP drafted the manuscript. JN and RJL will conduct the statistical analysis. DE will conduct the cost-effectiveness analysis. AC and RL advise on any DCD-related issues. All authors have read and approved the final manuscript. AHD acts as guarantor.

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Disclaimer The design, management, analysis and reporting of the study are entirely independent of J P Moulton Charitable Foundation and NHSBT.

Competing interests AC and RL are affiliated to NHSBT, which provided the DCD allografts free of charge. The current version of the protocol is V.9.0. The study commenced recruitment in October 2019. Imperial College London is the main sponsor for this study. Delegated responsibilities are assigned to the NHS trusts taking part in this study.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

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